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Pharmaceutical Discharges and Drinking Water

Current Good Manufacturing Practices, Emission Regulations, and Guidances Minimize or Prevent Pharmaceutical Discharges from Entering our Sources of Drinking Water

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Manufacture of Pharmaceutical Chemicals

- **Manufacture of pharmaceutical finished dosage forms (drug products) normally takes place in two stages. They are 1) the synthesis/manufacture (using raw materials and synthesis intermediates) of API or bulk drug; and 2) the manufacture of the finished drug product (using the API and excipients).**

- **FDA requires accountability for various components of APIs or drug product during manufacture through comparison of actual yields with theoretical yields under the cGMP regulations (6,7).**

    - EPA regulates the emissions and effluent discharges from pharmaceutical manufacturing. The Federal Water Pollution Control Act (Clean Water Act) amendments of 1972 established a comprehensive program to “restore and maintain the chemical, physical and biological integrity of the Nation’s waters”, under which EPA issued effluent limitation guidelines, pretreatment standards, and new source performance standards for industrial discharges.

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- The regulations (EPA, September 21, 1998) for effluent limitation guidelines for the pharmaceutical manufacturing point source category are described in 40 CFR Parts 136 and 439 titled “Pharmaceutical Manufacturing Category Effluent Limitations Guidelines, Pretreatment Standards, and New Source Performance Standards; Final Rule” (8).

- Compliance with FDA and EPA mandated regulations/guidances may preclude or minimize any significant release of pharmaceutical chemicals into the environment during manufacture.

Human Use of Pharmaceutical Chemicals

- Under the NEPA mandate (21 CR Part 25) Environmental Assessment Reports (EAs) supported by experimental data were required by FDA for all drugs as a part of the New Drug Applications (NDAs) for approximately 10 years (~1985 to 1995).

- In 1995, the data on the fate and effects of several hundred pharmaceutical chemicals generated during this period was reviewed by FDA (*9*), and based on these data FDA reevaluated and revised its environmental regulations (10) for human drugs.

Human Use of Pharmaceutical Chemicals

- Since 1998, as per this guidance, applicants are required to provide an EA when the expected introduction concentration (EIC) of the active ingredient of the drug in the aquatic environment (EIC-Aquatic) exceeds one part per billion (1 ppb).
- Applicants were granted categorical exclusions from EA requirements if the EIC-aquatic was <1 ppb.

Human Use of Pharmaceutical Chemicals

- The EIC at the point of entry into the aquatic environment in ppb is calculated by the following equation provided in FDA guidance (*10*): A x B x C x D, where, A = kg/year produced for direct use as active moiety (maximum production/year in a five-year production cycle based on marketing estimates); B = 1/liters per day entering POTW, estimated at 1.214×10^{11} (from the 1996 Needs Survey by the EPA); C = year/365 days; and D = 10^9 μg/kg (conversion factor).

Human Use of Pharmaceutical Chemicals

- Based on this equation, EIC-aquatic of 1 ppb = 44,300 kg of active ingredient of drug /year.
- Yearly production of majority of human health drugs is much below this cut-off point of 44, 3000 kg.
- Categorical exclusions from EA are normally granted if the EIC is <1 ppb.

Disposal of Pharmaceutical Chemicals

- The disposal of unused, expired or returned APIs or drug products are scrutinized under material accountability of cGMP regulations.

- As stated in cGMPs, records of returned APIs, intermediates, drug products should be maintained and should include the name, batch or lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition.

Disposal of Pharmaceutical Chemicals

- Under the ultimate disposition status to destroy, a majority of the pharmaceutical compounds are disposed of through incineration or landfilling in a certified incinerator or landfill, respectively, both disposal methods designed to contain the exposure of residues to the aquatic or terrestrial environment.

- Hospitals, pharmacies, and clinics dispose empty or partially empty packages by collecting in appropriate containers and ultimate disposition through certified landfill or incinerator.

Disposal of Pharmaceutical Chemicals

- Expired drug products are generally returned to the manufacturer or distributor, either of whom may dispose the drug either through landfilling or incineration.
- At homes, empty or partiality empty containers are disposed through solid waste management systems, which include predominantly disposal in certified landfills. Domestic waste from pets, containing drug residues is similarly disposed into landfills.
- Therefore, disposal of pharmaceutical drugs is largely regulated and contained, eliminating this source as a contributor of pharmaceutical discharges into the environment.

Conclusions - Pharmaceutical Chemicals

- Compliance with FDA cGMP regulations and FDA and EPA regulations and guidances currently in place for pharmaceutical chemical discharges from manufacture, use and disposal prevent or minimize pharmaceutical drugs from entering sources of drinking water in the United States and causing any risk to human health.

- The authors believe that neither additional treatment of drinking water sources over and above existing now, nor new regulations are required.

Conclusions - Pharmaceutical Chemicals

- In the rare event of pharmaceutical chemical residues being detected in drinking water supplies, using available analytical technologies, establishment of a clear cause and effect relationship investigations are required, to explain unusual circumstances that may have resulted in the detection of such residues and their impact on human health.
- The unusual circumstances may include non-compliance with existing regulations or accidental discharges.

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